Botulinum toxin therapy in amputee pain management

A scoping review

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ABSTRACT

Background: Post-amputation pain is common, occurring in up to 85% of patients. The pain can be related to the etiology of amputation, post-surgical healing, or prosthetic use. Pain syndromes may arise from a variety of tissue pathologies and can be broadly categorized into residual limb pain (RLP) or phantom limb pain (PLP). Botulinum toxin (BTX) has been found to be effective in treating a variety of neuropathic pain conditions. This scoping review summarizes the use of BTX in RLP and PLP management of patients with a major extremity amputation.

Methods: A literature search was conducted using PubMed, Web of Science, Cochrane Library, Scopus, and Google Scholar. Sixteen studies were included. Most studies excluded did not address BTX use in amputee pain management. Extracted data were categorized by either RLP or PLP.

Results: Two randomized controlled trials (RCTs), 10 case series, and 4 case reports were included (total 68 patients, 82 amputations). Seven studies addressed BTX use in both RLP and PLP, 5 studies address RLP exclusively, and 5 additional studies exclusively addressed PLP. Toxin types, injection techniques, and dosages varied between the studies. Negative results were reported in 2 RCTs and 2 case series showing 30% of patients with RLP and 50% patients with PLP did not benefit from BTX.

Conclusion: Literature for BTX in PLP and RLP is broad but lacking rigour for definitive conclusions to guide usage. There were more positive results for BTX use in RLP than in PLP. Case reports and patient series show promising results for both PLP and RLP, indicating future research should be directed at adequately-powered prospective trials.

INTRODUCTION

Post-amputation pain is a major concern in the amputee population, as it impedes rehabilitation and interferes with quality of life.¹ It is estimated to affect up to 85% of patients^{2,3} and remains a challenging condition to treat, often requiring a multimodal approach to pain control. Post-amputation pain can be broadly categorized into residual limb pain (RLP) or phantom limb pain (PLP). There is a strong correlation between RLP and PLP, with patients often having difficulty distinguishing one category from another.⁴

Residual limb pain has multiple etiologies, both neuropathic and nociceptive. These may include but are not limited to: infection (osteomyelitis, cellulitis), failure of flap closure, vascular

insufficiency/claudeication, bone spurs, heterotopic ossification, unusual mechanical stress at prosthesis-residual limb interface, soft tissue inflammation around the prosthesis from improper prosthetic fit, stump bursitis, neuroma, complex regional pain syndrome, cutaneous lesions (abrasions, ulceration, folliculitis, and eczema), and painful muscle contractions or dystonias.⁵

Phantom limb pain typically occurs within the first 6 months after a limb amputation and can last several years after the amputation in the distribution of the amputated limb. Its description varies from neuropathic-like characterizations such as sharp, shooting, or electrical-like, to more nociceptive-like descriptions such as dull, squeezing, or cramping.⁶ The mechanism underlying phantom pain perception remains poorly understood, but it is thought to involve supraspinal, spinal, and peripheral mechanisms.⁷ Current treatment modalities attempt to target one or more of these areas to achieve pain control. For example, mirror therapy, deep brain stimulation, guided imagery/biofeedback/hypnosis, and opioids/anticonvulsants attempt to target somatosensory cortical reorganization in phantom limb pain.⁷ In addition, spinal cord stimulation targets functional changes in the dorsal horn of the spinal cord after deafferentation from a peripheral nerve injury.⁶ Finally, injections with local anesthetic or botulinum toxin, pulsed radiofrequency, or peripheral nerve stimulation attempt to target peripheral mechanisms such as neuroma formation, in which afferent fibers can develop ectopic activity, mechanical sensitivity, and chemosensitivity to catecholamines.⁶

Botulinum toxin (BTX) is a potent substance derived from *Clostridium botulinum* bacteria and has been used for a variety of medical conditions, most commonly in disorders of excessive muscle contraction. Its benefit lies in its interference with acetylcholine neurotransmitter release at the neuromuscular junction by cleaving proteins in the Soluble N-ethylmaleimide-sensitive factor Attachment protein REceptor (SNARE) complex at the presynaptic nerve terminal, leading to decreased muscle contraction.^{8,9} In addition, BTX has been found to be effective in treating a variety of neuropathic pain conditions, but its antinociceptive effect remains unclear.^{8,9} Its effect on neuropathic pain appears to be independent from its effect on muscle contraction, with postulated mechanisms involving inhibition of SNARE complex-mediated vesicular release of substance P and glutamate, as well as reduction in vanilloid receptor activity involved in integrating noxious stimuli.⁹

There are seven types of toxins recognized, labeled A through G. Current BTX formulations include onabotulinumtoxinA (Botox®, Allergan Inc., Irvine, CA, USA), abobotulinumtoxin A (Dysport®, Ipsen Ltd., Berkshire, UK), incobotulinumtoxinA (Xeomin®, Merz, Frankfurt, Germany, and Prosigne®, Lanzhou Institute, Lanzhou,

China), and rimabotulinumtoxinB (MyoBloc®, Malvern, PA, USA and NeuroBloc®, Elan Pharmaceuticals, San Diego, CA, USA). The formulations differ in production and potency.^{8,9}

Although there have been a multitude of trials studying the use of BTX in neuropathic and nociceptive pain,^{8,9} there are currently no guidelines for the use of BTX in post-amputation pain, and studies are mostly limited to case reports and small case series. In this scoping review, the current available literature on the use of BTX in post-amputation pain will be summarized, with the goal of providing context for future adequately-powered prospective trials to guide BTX usage in post-amputation pain.

METHODS

A literature search from 1996 to 2016 was conducted using the following databases: PubMed, Web of Science, Cochrane Library, Scopus, and Google Scholar.

The following search terms were used: Botox; botulinum; BoNT; BTX; amputee; amputation; stump; residual limb; phantom; limb deficiency. All citations from relevant articles were checked to identify additional relevant sources. Boolean search operators were used: ((Botox OR botulinum OR BoNT OR BTX)) AND ((amputee OR amputation OR stump OR residual limb OR phantom OR limb deficiency)).

Inclusion criteria included: English abstract; human studies; use of BTX for pain management in major extremity amputation or congenital limb deficiency proximal to wrist or ankle.

RESULTS

A total of 79 unique records were obtained. After inclusion criteria were applied, 16 studies were included in this scoping review (2 randomized controlled trials (RCTs),^{10,11} 10 case series,^{12-19,22,23} and 4 case reports^{20,21,24,25}), including 6 abstracts (1 meeting abstract,¹⁶ 2 poster abstracts,^{21,24} and 3 foreign language articles with English abstracts^{12,20,22}). Of these, 8 studies assessed outcomes of BTX use in both PLP and RLP (2 RCTs,^{10,11} 5 case series,¹³⁻¹⁷ and 1 case report²⁰), 4 studies addressed RLP only (3 case series,^{12,18,19} 1 case report²¹), and 4 additional studies addressed PLP only (2 case series,^{22,23} 2 case reports^{24,25}). The study results are summarized in Table 1 and Table 2 for RLP and PLP respectively. Table 3 shows aggregated demographic data, with the exception of one case series for which demographic data were not available from its published meeting abstract.¹⁶

DISCUSSION

Although all 16 included studies evaluated the effects of BTX on post-amputation pain, there was a notable variation in the emphasis on pain management between each study. For example, it should be noted that 6 studies^{10,12-15, 24} evaluated the reduction in residual limb hyperhidrosis as the primary outcome of interest with BTX treatment; residual limb pain and/or phantom limb pain were secondary variables. However, given the limited literature on using BTX therapy to treat post-amputation pain, RLP and PLP results from the quoted studies were included in the analysis to achieve a comprehensive scoping review.

Due to the heterogeneity of primary outcomes in the included studies, there was a wide range of toxin serotypes, total administered toxin dose, and injection techniques. Toxin serotypes included rimabotulinumtoxinB (NeuroBloc®, MyoBloc®), onabotulinumtoxinA (Botox®), abobotulinumtoxinA (Dysport®), unspecified botulinum toxin type A (BTX-A) and unspecified botulinum toxin type B (BTX-B). The majority of studies used varying formulations of the more widely studied BTX-A; only 4 of 16 studies evaluated the use of BTX-B. Of note, 2 of 6 studies that focused on the treatment of residual limb hyperhidrosis as the primary outcome used BTX-B.^{10,13} There appears to be a similar variety of the toxin serotypes between positive and negative studies for RLP or PLP.

In studies focusing on hyperhidrosis as the primary outcome,^{10,12-15,24} BTX injections were generally performed intradermally in a grid pattern ranging from 1 cm² to 6 cm². Positive results in post-amputation pain management were seen in 50% of these studies.^{12,13,24} In the remaining studies focusing on post-amputation pain as the primary outcome, BTX injections were primarily performed intramuscularly in trigger points. Of note, 100% of these studies showed positive results.^{16-20,22,23} Intraneuroma,¹¹ perineuroma,²⁵ and subcutaneous¹¹ injections were also described, also with positive results in post-amputation pain.

Total doses for BTX-A ranged from 100 units intramuscularly, or 200 to 500 units intradermally. Total doses for BTX-B ranged from 2500 to 5000 units intramuscularly, or 1750 to 20000 units intradermally. There did not appear to be an obvious relationship between dosage and efficacy of BTX-A or BTX-B for post-amputation pain, but there may be more benefit in intramuscular administration rather than intradermal administration despite the lower dosages used in intramuscular administration. One RCT used relatively large dosages of 10000 to 20000 units of intradermal BTX-B,¹⁰ with lack of positive findings in post-amputation pain management despite positive findings seen in observational studies at lower dosages of BTX-B at 1750 units intradermally and 2500 to 5000 units intramuscularly.^{13,16,18} Conversely, another RCT used moderate dosages of 250 to 300 units of BTX-A intramuscularly, subcutaneously, and intraneuroma, leading to some improvement in RLP.¹¹ This is in contrast to a case series that used higher dosages of 300 to 500 units of BTX-A intradermally and found no significant improvement in post-amputation pain,¹⁴ while studies that used lower dosages of 100 units BTX-A intramuscularly showed benefit in post-amputation pain.^{16,17,19,20}

Outcome measures in all studies was dependent on patient reporting via pain severity scoring systems, including visual analog scales (VAS), numeric rating scales (NRS), and Likert scales. Based on these outcome measures, beneficial results of BTX treatment for post-amputation pain were seen in several observational studies. For example, in one case series, patients' PLP severity decreased from 9 to 2 on a 10-point VAS for up to 12 weeks after abobotulinumtoxinA (Dysport®) intramuscular injections (200 to 500 units), allowing for better prosthesis tolerance and use.²³ A case report showed reduction of pain medication such as intrathecal morphine by 40% at 12 months of quarterly injections with 100 units

of onabotulinumtoxinA (Botox®) and elimination of all other pain medications, remaining “almost pain-free”.²⁰ Kern and colleagues have also described a reduction of postamputation pain by 60% to 80% in 4 patients, with a 50% to 90% reduction in pain attack frequency such as from monthly to weekly, and a reduction in pain duration from 120 minutes to 10 minutes per day.^{18,22} In another case report, PLP ceased within 4 weeks of BTX injection, and the patient remained pain-free at the 1-year followup.²⁴

Despite these positive results, from this scoping review, 30% of patients with RLP (19 patients of 62), corresponding to 37.5% of amputations (27 amputations of 72) did not benefit from BTX. In patients with PLP, 50% of patients (23 patients of 46), corresponding to 57% of amputations (31 amputations of 54) did not benefit from BTX. These negative PLP results stem from 2 RCTs^{10,11} and 2 case series of 8 and 4 patients respectively.^{14,15} However, the 2 RCTs were limited in sample size and may not have been adequately powered. For instance, the study by Pasquina *et al* with 7 subjects in the BTX study arm did not comment on power calculations,¹⁰ while the study by Wu *et al* acknowledged the small sample size of 4 subjects in the BTX study arm limited the study’s power. It should also be noted that the results from one case series with positive results for BTX use in post-amputation pain were not included in the data analysis, as the number of subjects in the study was not published.¹⁶

CONCLUSIONS

These data suggest there is more evidence for the use of BTX in RLP than in PLP, and more evidence for intramuscular injection technique than intradermal injection technique. However, this evidence is limited to pooled data from case reports and small case series, some of which measured BTX effects on pain, prosthesis use, and function as secondary outcomes. Therefore, there is a need for larger RCTs or systematic reviews to study the effect of BTX on post-amputation pain. BTX appears to have the potential to provide post-amputation pain relief, and may facilitate more effective amputee rehabilitation by offering one aspect of the multi-modal approach to amputee pain management.

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FEATURE ARTICLE

Table 1. Summary of studies incorporating botulinum toxin (BTX) use in residual limb pain (RLP).

Study Author (Year)	Study Design	Subjects, No. (Amp., No.)	Toxin Serotype (Commercial name)	Total Dose, Units	Injection Site (Pattern)	Outcome Measures	Results
Pasquina et al ¹⁰ (2016)	RCT	7 (11) in BTX study arm	rimabotulinumtoxinB (MyoBloc [®])	10000 to 20000	Intradermal (4 cm ² to 6 cm ² grid)	RLP reduction (100 mm VAS)	Negative (p>0.05)
Wu et al ¹¹ (2012)	RCT	6 (6) in BTX study arm (of 7 (7) in BTX arm)	onabotulinumtoxinA (Botox [®])	250 to 300	Intramuscular, subcutaneous, or intraneuroma	RLP reduction (0 to 10 VAS)	Improvement in both groups (Botox: p<0.002, Lidocaine/Depomedrol p<0.06) at 1 month. Botox p<0.59, Lidocaine/Depomedrol p<0.96 at 6 months
Alvarez-Sala et al ¹² (2012)	Case series	14 (14)	onabotulinumtoxinA (Botox [®])	100 to 200	Intradermal (2 cm ² grid)	RLP reduction (0 to 100 VAS)	RLP decreased (p<0.005)
Kern et al ¹³ (2011)	Case series	9 (9)	rimabotulinumtoxinB (MyoBloc [®])	1750	Intradermal (2 cm ² to 4 cm ² grid)	RLP reduction (0 to 10 NRS)	RLP significantly reduced after 3 months ((NRS 3 from baseline NRS 5), p=0.008)
Charrow et al ¹⁴ (2008)	Case series	8 (8)	BTX-A (Unspecified)	300 to 500	Intradermal (1 cm ² grid)	RLP reduction (10-pt Likert scale)	Negative (p = 0.89)
Trull et al ¹⁵ (2011)	Case series	4 (8)	onabotulinumtoxinA (Botox [®])	200 to 300	Intradermal (1 cm ² grid)	RLP severity (7-pt Likert scale)	Negative study: Paper claims "no effect on RLP"; RLP decreased by 1.5 +/- 0.6 on Likert scale
Kern et al ¹⁶ (2004)	Case series	unknown	onabotulinumtoxinA (Botox [®]) or BTX-B	100 BTX-A or 5000 BTX-B	Muscle trigger points (4 to 5 points)	RLP reduction (pain diary)	Post-amputation pain reduced by 60 to 80% in most cases
Kern et al ¹⁷ (2004)	Case series	4 (4)	BTX-A (Unspecified)	100	Muscle trigger points (unspecified pattern)	Patient-reported RLP reduction (0 to 10 NRS)	Case 2: RLP decrease lasted 3 months and resulted in day-long prosthesis use. Case 4: RLP decrease from NRS 6 to 0 lasted 10 weeks, leading to better prosthesis tolerance
Kern et al ¹⁸ (2004)	Case series	4 (4)	rimabotulinumtoxinB (NeuroBloc [®])	2500 to 5000	Muscle trigger points (unspecified pattern)	RLP reduction (0 to 10 VAS)	Decreased RLP for 4 to 12 weeks (all cases); Case 2: VAS 4.5 to 1.5 (average pain), VAS 10 to 2 (max pain). Pain frequency and duration decrease (weekly to monthly, hours to minutes). Case 3: RLP VAS 5 to 0.5, 50% frequency. Case 4: RLP VAS 5 to 2 (average pain), 7 to 3 (max pain)
Kern et al ¹⁹ (2003)	Case series	4 (4)	onabotulinumtoxinA (Botox [®])	100	Muscle trigger points (unspecified)	RLP reduction (0 to 10 VAS)	Case 1: VAS 9.5 to 6.5. Case 2 to 4: no RLP for 3 months; repeat BTX same results
Kern et al ²⁰ (2004)	Case report	1 (1)	onabotulinumtoxinA (Botox [®])	400 (100 every 3 mo. for 1 y)	Muscle trigger points (unspecified pattern)	RLP reduction (0 to 10 VAS)	Almost pain-free after 12 months; intrathecal morphine reduced to 40% initial dose, all pain treatments ceased
Nguyen et al ²¹ (2016)	Case report	1 (2)	onabotulinumtoxinA (Botox [®])	Unspecified	Unspecified	RLP reduction as per patient reporting	Decrease in stump pain due to decreased muscle spasms.

VAS = visual analog scale; NRS = numeric rating scale; Amp = Amputations

Table 2. Summary of studies incorporating botulinum toxin (BTX) use in phantom limb pain (PLP).

Study Author (Year)	Study Design	Subjects, No. (Amp., No.)	Toxin Serotype (Commercial name)	Total Dose, Units	Injection Site (Pattern)	Outcome Measures	Results
Pasquina et al ¹⁰ (2016)	RCT	7 (11) in BTX study arm	rimabotulinumtoxinB (MyoBloc [®])	10000 to 20000	Intradermal (4 to 6 cm ² grid)	PLP reduction (100 mm VAS)	Negative (p>0.05)
Wu et al ¹¹ (2012)	RCT	4 (4) PLP in BTX study arm (of 7 (7) in BTX arm)	onabotulinumtoxinA (Botox [®])	250 to 300	Intramuscular, subcutaneous, or intraneuroma	PLP reduction (0 to 10 VAS)	No improvement in either group (Botox: p=0.49; Lidocaine/Depomedrol: p=0.42)
Kern et al ¹³ (2011)	Case series	9 (9)	rimabotulinumtoxinB (MyoBloc [®])	1750	Intradermal (2 to 4 cm ² grid)	PLP reduction (0 to 10 NRS)	Decreased PLP severity after 3 months (NRS 3 from baseline 5, p=0.008)
Charrow et al ¹⁴ (2008)	Case series	8 (8)	BTX-A (Unspecified)	300 to 500	Intradermal (1 cm ² grid)	PLP reduction (10-pt Likert scale)	Negative (p = 0.39)
Trull et al ¹⁵ (2011)	Case series	4 (8)	onabotulinumtoxinA (Botox [®])	200 to 300	Intradermal (1 cm ² grid)	PLP severity (7-pt Likert scale)	Negative study: Paper claims "no effect on PLP"; PLP decreased by 1.5 +/- 0.6 on Likert scale
Kern et al ¹⁶ (2004)	Case series	unknown	onabotulinumtoxinA (Botox [®]) or BTX-B (Unspecified)	100 BTX-A or 5000 BTX-B	Muscle trigger points (4 to 5 points)	PLP reduction (pain diary)	PLP disappeared completely for 2-3 months. Painfree for >1 year with 4 injections (1 patient).
Kern et al ¹⁷ (2004)	Case series	4 (4)	BTX-A (Unspecified)	100	Muscle trigger points (unspecified pattern)	Patient-reported PLP reduction (0 to 10 NRS)	Case 1: "pronounced reduction in PLP"
Kern et al ²² (2003)	Case series	4 (4)	onabotulinumtoxinA (Botox [®])	100	Muscle trigger points (unspecified pattern)	PLP reduction in pain frequency, duration, intensity (0 to 10 VAS)	PLP reduced by 60 to 80% in all cases. 90% reduction in pain frequency (3 patients). Pain duration shortened from 120 min to 5 to 10 min and pain intensity reduction from VAS 9 to 1 to 2 (2 patients).
Jin et al ²³ (2009)	Case Series	3 (3)	abobotulinumtoxinA (Dysport [®])	200 to 500	Intramuscular (4 to 12 points)	PLP reduction (0 to 10 VAS, CGI)	Response within 3 to 4 days and marked improvement for up to 11 weeks, allowed for reduction of pain medications in all cases. Case 1 VAS 9 to 10 to 0 to 2, Case 2 VAS 7 to 10 to 1 to 3, Case 3: VAS 6 to 8 to 1 to 2.
Kern et al ²⁰ (2004)	Case report	1 (1)	onabotulinumtoxinA (Botox [®])	400 (100 every 3 mo. for 1 y)	Muscle trigger points (unspecified pattern)	PLP reduction (0 to 10 VAS)	Almost pain-free after 12 months; intrathecal morphine reduced to 40% initial dose, all pain treatments ceased
Poluri et al ²⁴ (2006)	Case report	1 (1)	BTX-A (Unspecified)	100	Intradermal (1 cm ² grid)	PLP reduction as per patient report	PLP ceased within 4 weeks of BTX injection, up to 1 year at followup.
Tyvaert et al ²⁵ (2009)	Case report	1 (1)	BTX-A (Unspecified)	30	Surrounding the amp. scar	PLP reduction as per patient report	Reduced PLP severity up to 14 weeks from BTX injection.

CGI = global clinical improvement based on a 0-3 scale (0 = no effect, 3 = marked improvement); VAS = visual analog scale; NRS = numeric rating scale; Amp = Amputations

Table 3. Summary of study subject characteristics.

	RLP	PLP	All Post-amputation Pain (RLP + PLP)
Studies, No.	11	11	15
Subjects, No.	62 (10F, 50M, 2 unknown)	46 (8F, 37M, 1 unknown)	68 (13F, 52M, 3 unknown)
Amputations, No.	72	54	82
Age, mean (SD), y	44 (14), n=60	40 (14), n=42	44 (14), n=68
Time post-amputation, mean (SD), y	3 (5), n=34	4.4 (7.1), n=37	4.4 (6.7), n=42
Amputation level, ^a No. (%)	Transfemoral, 29 (40) Transtibial, 37 (51) Symes, 1 (1.5) Transradial, 2 (3) Transhumeral, 2 (3) Transmetatarsal, 1 (1.5)	Transfemoral, 21 (39) Transtibial, 28 (51) Symes, 1 (2) Transradial, 1 (2) Transhumeral, 1 (2) Above shoulder, 1 (2) Unknown, 1 (2)	Transfemoral, 32 (40) Transtibial, 41 (51) Symes, 1 (1) Transradial, 2 (2) Transhumeral, 2 (2) Above shoulder, 1 (1) Transmetatarsal, 1 (1) Unknown, 1 (2)
Amputation etiology, ^b No. (%)	Traumatic, 44 (61) Infectious, 6 (8) Arterial occlusive disease, 13 (18) Unknown, 9 (13)	Traumatic, 41 (76) Infectious, 1 (2) Arterial occlusive disease, 7 (13) Unknown, 5 (9)	Traumatic, 50 (61) Infectious, 6 (7.5) Arterial occlusive disease, 15 (18.5) Unknown, 11 (13)

^a Amputation level was known for 62 subjects (72 amputations) in RLP, and for 45 subjects (53 amputations) for PLP.

^b Amputation etiology was known for 55 subjects (63 amputations) in RLP, and for 41 subjects (49 amputations) for PLP.

Legend for Table 3: y = years; No. = number; SD = standard deviation; F = females; M = males; n = number of subjects for which respective data were known